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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,534	UMEDA ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7-14 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-14 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 09/11/2008 and a supplemental response filed on 02/26/2009 in response to office action mailed on 05/15/2008 has been acknowledged.

Claim 1, 3, 4, 7-11, and 14 are amended.

Claim 25 is new.

Claim 2 is canceled.

Claims 1, 3, 4, 7-14, and 23-25 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

Applicants arguments in the response filed on 09/11/2008 & 02/26/2009 are fully considered while writing this action.

Withdrawn: Claims 1-3, 8-12, 14 and 23 rejection under 35 U.S.C. 102(b) as being anticipated by Itoh et al. (1993) J. Cell Biol. 121:491-502 (made of record in the IDS filed 13 February 2006) as evidenced by Fermentas Life Sciences (2006) "pBluescript II KS(+/), pBluescript II SK(+/-): description & restriction map description & restriction map" downloaded from www. fermentas. com /techinfo /nucleicacids /mappbluescriptiiskks.htm, 12 May 2008 for the reasons of record set forth in the office action mailed on 05/15/2008 is withdrawn in view of Applicants amendments to claims.

Withdrawn: Claims 1-4, 7-14, 23 and 24 rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the office action mailed on 05/15/2008 is withdrawn in view of Applicants amendments to claims.

Claim Objections

Claim 8 is objected-to as it recites on line 2 “comprises in the upstream of an exogenous gene a promoter” makes the claim language awkward. Changing the same to recite “comprises an exogenous gene operatively linked to a promoter” is suggested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 7-12, 14,23 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (1994) Scientific American 270:34-41 in view of Itoh et al. (supra). For the reasons of record as set in the office action mailed on 05/15/2008 and modified as below.

The claims are directed to a gene targeting vector for introducing an exogenous gene into the ZO-1 gene region in a non-human mammal without affecting cellular function, wherein the vector comprises the exogenous gene inserted between a first and a second ZO-1 gene fragments that are arranged in the same order as that of native ZO-1 gene. In further limitations ZO-1 gene fragments comprise exon II or a portion thereof, the vector is used for generating a gene targeted non-human mammal or a mammalian cell, the exogenous gene is operatively linked to a promoter, at he vector comprises a marker gene that can include a drug resistance marker, the drug resistance marker is β-geo, the targeted non-human mammal is a mouse.

Capecchi teaches transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi further teaches that such disruptions are produced using targeting vectors comprising first and second polynucleotide sequences homologous to the target gene and a selectable marker (see especially the drawing at the top of page 36 and the caption thereto). Capecchi differs from the claimed invention in that the targeting construct does not disrupt the ZO-1 gene

gene. However, at the time the claimed invention was made, Itoh et al. had disclosed the cloning of the mouse ZO-1 gene.

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to make a targeting vector for a disruption in a targeted gene as taught by Capecchi wherein the gene was the ZO-1 gene as taught by Itoh et al. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the ZO-1 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. See, e.g., teachings of Capecchi such as, "Gene targeting offers investigators a new way to do mammalian genetics—that is, to determine how genes mediate various biological processes. This technique was needed because the classical methods of genetics, which have been highly successful in analyzing biological processes in simpler organisms were not readily adaptable to organisms as complex as mammals" (first full paragraph on page 35). In view of this, one of ordinary skill in the art would have been sufficiently motivated to produce a targeting vector comprising sufficient sequence from a mouse ZO-1 gene to target the vector into the mouse ZO-1 gene and an exogenous selectable marker in order to disrupt the gene in a mouse characterizing the roles of ZO-1 in mammalian biological processes.

Thus, the invention as a whole, would have been obvious to one of ordinary skill in the art at the time was made. In addition, the limitations of the dependent claims are also found in the art. Specifically, Capecchi teaches construction of a targeting vector wherein a neomycin resistance gene is inserted within an exon of the targeted gene and thymidine kinase resistance gene is inserted downstream of the neomycin resistance gene. (See the drawing on page 36 and the caption thereto.) This teaching, in view of the disclosure of a nucleic acid comprising the entire coding sequence from the mouse ZO-1 gene renders obvious the targeting vector of claims 2, 3, 7-12 and 23. For these reasons, the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC §103(a) as obvious over the art.

Claims 13 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (supra) in view of Itoh et al. (supra), as applied to claims 12 and 23 herein above, and further in view of Blake et al. (1997) BioTechniques 23:690-695.

Claims 13 and 24 are directed to the method of claims 12 and 23, respectively, wherein the drug resistance gene expression cassette is a DNA fragment comprising β-geo. As described above, the invention of claims 12 and 23, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Capecchi and Itoh et al. However, Capecchi teaches constructing targeting vectors comprising a neomycin resistance gene rather than a β-geo resistance gene.

Blake et al. teaches a marker gene comprising a fusion of the beta-galactosidase and neomycin resistance marker genes (i.e., β-geo; see especially Figure 1 and the caption thereto) and teaches that the marker gene is useful for identifying cells expressing transgenic or gene targeted constructs in vivo. (See especially the final sentence of the Abstract and page 695, lines 21-25.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β-geo marker gene of Blake et al. for the neomycin resistance gene in the targeting vector of Capecchi in view of Itoh et al. In KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (Id. At 1395.)

In the instant case, the targeting vector of Capecchi in view of Itoh et al. differs from the presently claimed invention only in the substitution of a neomycin resistance marker gene for the β-geo marker gene recited in the claims. However, the β-geo marker gene and its use as a marker in gene targeting constructs was known in the art at the time the instant invention was made. Therefore, one could have substituted the β-geo marker for the neomycin resistance gene used in the targeting vector of Capecchi in view of Itoh et

al. with the predictable outcome being a targeting vector useful in the construction of mice comprising targeted disruptions in the ZO-1 gene.

As the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of invention, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Response to Applicants arguments of 05/15/2008:

The Applicant argues the invention is not obvious because Capecchi does not teach ZO-1 gene targeting and instead he teaches targeting of HoxA-3 gene. The Applicant further argues Itoh reference is not relevant because Itoh does not teach an exogenous gene inserted between ZO-1 gene fragments. Still further, the Applicant argues Blake does not cure the defects of Capecchi and Itoh et al because it is not obvious to replace the neomycin resistance marker gene with a β-geo marker gene.

The Applicants arguments are however, found not persuasive because the combination of Capecchi and Itoh references as well as Capecchi, Itoh and Blake references in the light of available technical and scientific knowledge in relevant prior art, as espoused above, clearly teach all the elements and limitations of instant claims The Applicant further should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). Hence the obviousness rejection as promulgated above is maintained.

Double Patenting Warning

Applicant is advised that should claim 1 be found allowable, claim 7 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 7 requires the use of the vector for generating non-human mammal expressing an exogenous gene, however, such depends from Claim 1, which requires the introducing the gene in to the non-human mammal, Claim 7 is a substantial duplicate of Claim 1.

Applicant is advised that should claim 13 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 13 that depends from claim 12 which in turn depends from 9 that is limiting from base claim 1 requires the use of drug resistance gene expression cassette having β–geo gene. Similarly claim 24 requires the β–geo gene and as such depends ultimately from base claim 1. Thus claim 24 is a substantial duplicate of Claim 13.

Conclusion:

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at **(800) 786-9199.**

/Robert M Kelly/
Primary Examiner, Art Unit 1633